Exercise and cystic fibrosis

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INTRODUCTION

Physical exercise is recognized to have considerable clinical benefit for different disease processes[1]. Regular habitual activity is cardioprotective and associated with a reduced morbidity and mortality for established cardiovascular disease[2,3]. Pulmonary rehabilitation programmes for patients with chronic airways obstruction (COAD), of which exercise is a core component, are being enthusiastically researched for their potential therapeutic benefit[4]. Although the short-term benefits of exercise have been established, whereby increased fitness improves morbidity and quality of life[5], there are no published prospective studies which report that regular exercise decreases mortality for patients with pulmonary disease. Exercise has been studied intensively in patients with cystic fibrosis (CF), yet its value has not been established to the degree that exercise must be adopted as an essential component of treatment. There needs to be scientific certainty about the short- and long-term benefits of exercise before it is incorporated into the already demanding regimen of daily self care of CF patients.

This review considers the current knowledge and future directions for the role of exercise in the therapy of cystic fibrosis.

PULMONARY RESPONSES AND LIMITS TO EXERCISE IN CF PATIENTS

In health and disease, the ability to exercise is related to the capacity of the cardiorespiratory system to deliver oxygen to working muscles and the efficiency of those muscles to extract and utilize the oxygen. Training induces physiological adaptations which allow individuals to perform a level of exercise more comfortably. Oxygen consumption (VO_2) is the most commonly used physiological measurement to monitor the level of fitness in sickness and in health following exercise training.

It can be defined as follows:

VO_2max=stroke volume × heart rate × arteriovenous oxygen difference

Maximum oxygen consumption (VO_2max) is the measurement made at an individual's peak work capacity (PWC) following a maximal exercise test. From this equation, it is apparent that the maximal oxygen consumption increases (improves) with training through several physiological adaptations. Stroke volume can increase with cardiac hypertrophy and chamber enlargement. More oxygen can be delivered to working muscles for a lower heart rate. With training, skeletal muscle undergoes structural and biochemical changes which permits a greater extraction and more efficient usage of oxygen delivered by the cardiorespiratory system.

During exercise ventilation increases from 5 l/min at rest to 180 l/min in the trained athlete. This is achieved by changes in tidal volume (V_T) and breathing frequency (fb) and adjustments in the duty cycle of breathing ($T_I \backslash T_{tot}$: the ratio of inspiratory time (Ti) to total breath duration) resulting in alterations to inspiratory ($V_T \backslash T_I$) expiratory flow rates. During progressive exercise, tidal volume can increase to 60% of the vital capacity; at this point the work of breathing increases disproportionately and subsequently minute ventilation increases by a rise in breathing frequency[6]. Inspiratory and expiratory times are balanced to increase V_T and allow the lungs to empty to maintain or reduce functional residual capacity. Consequently flow is maintained to preserve alveolar ventilation. These are important determinants of diaphragmatic contraction and position. Breathing patterns are adopted to minimize the sense of effort arising in the respiratory muscles in health and disease.

Exercise in health is limited by the symptoms of breathlessness or muscle fatigue. These symptom limits occur when muscle metabolism becomes oxygen depleted, enters the anaerobic phase and lactic acid accumulates. Lactic acidaemia stimulates a sharp increase in minute ventilation causing breathlessness and oxygen deprived muscles to fatigue. The work of anaerobic exercise becomes uncomfortable and stops. Training delays the onset of lactic acid accumulation[7] and increases the duration of aerobic exercise. Normally exercise is not limited by ventilation but patients with pulmonary disease (young and old) are ventilatory limited by the degree of severity of their lung disease.

Lung disease in cystic fibrosis is initiated by mucus plugging of the small airways. Bacterial infection of the mucus causes chronic inflammatory damage to the bronchioles. The early radiological changes indicating disease are hyperinflation and areas of atelectasis. These

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changes are parallelled by the earliest observed abnormality of pulmonary function in CF; an increase in the physiological dead space which increases with disease severity[8]. Ventilation is therefore higher for a given workload and the majority of CF patients with mild to moderate lung disease (FEV_1% predicted >60%) can exercise and train safely with the same intensity as their healthy peers, but similar levels of maximal oxygen consumption and peak work capacity may not be achieved. In cystic fibrosis, progressive airways obstruction reduces the vital capacity, limiting the compensatory increase in tidal volume during exercise with a resulting increase in the physiological dead space. The pulmonary pathology which disorders the relationship between gas exchange and ventilation in cystic fibrosis can be measured during exercise testing by the changing ratio of the physiological dead space (V_D) and tidal volume (V_T). In health and patients with mild lung disease, the V_D/V_T ratio which at rest is 25–35%, falls during exercise. In CF patients with severe disease this ratio is high at rest and increases with exercise due to poor matching of ventilation and perfusion and a limited tidal volume.

During exercise minute ventilation must be maintained to preserve the inspiratory and expiratory flow rates. This is achieved by two compensatory mechanisms; an increase in end-expiratory lung volume (EELV) and a decrease in inspiratory time (T_I)[9,10]. Airways obstruction causes prolongation of expiratory flow and in association with an increased breathing frequency results in air trapping. The consequence of the air trapping is to compromise effective functioning of the inspiratory muscles by flattening of the diaphragm and shortening the accessory and intercostal muscles. The compensatory mechanism exaggerates this situation. The work and oxygen cost of breathing are increased. It is the work of breathing at high lung volumes rather than changes in breathing patterns which increase the oxygen cost of breathing[11]. During maximal exercise the respiratory muscles may utilize 35–40% (normal 10–15%) of whole body oxygen consumption[12]. More respiratory work is performed during inspiration. If the inspiratory muscles are disadvantaged or overworked they will fatigue prematurely during progressive exercise.

As respiration during exercise becomes ventilatory limited, breathing patterns vary in order to maintain the continuation of comfortable breathing[13]. Coates *et al.* have studied this timing component of ventilation during progressive exercise in CF patients with severe airflow limitation[14]. In their study, the inspiratory time of some patients was reduced with an associated reduction in tidal volume. Although there was an increase in carbon dioxide this only occurred during the initial stages of exercise and did not imply the onset of respiratory failure. The adoption of this comfortable breathing pattern has also been described in older patients with chronic airflow limitation[15,16].

The duty cycle of breathing (T_I/Ttot) should also be related to the mouth pressure (Pm) required to sustain inspiratory flow. This can be expressed as the ratio of the inspiratory pressure for a given breath to maximal inspiratory pressure (MIP) reflecting the relative force required for inspiration. It follows if tidal volume is reduced by shortening the inspiratory time, the required pressure generated at the mouth (Pm) to sustain inspiration is lessened and consequently the oxygen cost of breathing. Altering breathing patterns in this manner may forestall muscle fatigue and permit more comfortable breathing[15].

An increased alveolar-arterial oxygen gradient is one of the early pathological changes to occur in cystic fibrosis[17]. An increase in ventilation-perfusion mismatch parallels disease severity and can result in oxygen desaturation during exercise. Although arterial oxygen desaturation occurs with severe disease during exercise (FEV_1 <35% predicted[18], resting oxygen saturation is a less predictable factor of oxygen desaturation during exercise for the majority of patients[19]. In patients with severe disease an increase or no change in oxygen saturation were more common than a decrease during exercise.

Pulmonary disease is the main contributing factor to exercise limitation in cystic fibrosis but poor nutritional status is also considered to be an independent contributory factor[20]. Although muscle strength has been reported as normal in CF patients[21,22], decreased muscle mass in the legs can reduce aerobic exercise performance on a cycle ergometer[23] suggesting that adequate nutrition may improve muscle mass and exercise performance. A recent study of diaphragmatic power in CF patients showed that strength decreased with disease severity and hyperinflation but malnutrition was the strongest indicator of diaphragmatic weakness[24]. No studies have been performed as to whether exercise training will delay respiratory muscle fatigue.

Although attention has focused on the progression of lung disease causing pulmonary hypertension, two-dimensional echocardiography has demonstrated an enlarged right ventricle compressing the left ventricle[25]. The result is a decreased left ventricular filling and a diminished stroke volume at rest which is exaggerated by exercise.

RECOGNIZED BENEFITS OF EXERCISE TRAINING IN CYSTIC FIBROSIS

The ability to sustain exercise comfortably is defined as fitness and the purpose of training is to increase the length of time during which comfortable exercise can be undertaken (endurance). It is with this intention that extensive research has been undertaken to assess the value of training and

exercise in CF patients. Although considerable useful information has resulted and been put into practice from these studies many questions remain. There is no published evidence in pulmonary disease as to whether long-term exercise influences mortality. More specifically, what is the most appropriate form of exercise and will patients remain sufficiently motivated to include it in their daily self care? Before considering the future directions which exercise programmes should assess, it is appropriate to evaluate current knowledge.

Two early studies reviewed the cardiorespiratory adjustments that take place during progressive exercise in CF patients with a spectrum of disease severity[26,27]. Patients with mild to moderate disease could exercise almost to the same level as controls in terms of peak minute ventilation, peak work rate and oxygen consumption, but patients with severe disease had a reduced work capacity, an exercise-induced arterial oxygen desaturation and an increase in end tidal carbon dioxide. Over the last decade, several supervised studies of general exercise training (running or cycling) have confirmed that CF patients with a range of disease severity can improve their exercise tolerance[28–32]. Specific features highlighted in these studies were an increase in respiratory muscle endurance[28], overall endurance[32], a reduction in residual volume[29], an increase in sputum expectoration associated with exercise training[30] and maintenance of pulmonary function[31].

The purpose of supervised training is to transfer this activity from the hospital to home. Two short studies have reported mixed results in successfully achieving this goal. Although an early study reported a decline in compliance with home exercise[33], a later study demonstrated an improvement in the activities of daily living through increased fitness[34]. One study has recorded a reduction in breathlessness following training which was independent of ventilation but associated with a reduction in residual volume as the only change in static lung function[35].

Athletes adopt specific training programmes to acquire fitness for their chosen discipline. The five elements of fitness consist of strength, endurance, flexibility, speed and skill. For respiratory disease, the most important component of fitness is to improve endurance. The ability to sustain comfortable exercise is more practically related to fulfilling the activities of daily living and therefore the quality of life. In a similar manner, flexibility and speed can be equated to increasing the mobility of the breathless unfit patient. The role of training muscles purely for strength in CF patients is unclear.

Training studies for CF patients initially evaluated general exercise programmes, but similar to athletes who seek to achieve fitness for a specific sport, research has scrutinized specific training of (i) the upper body muscles and (ii) the inspiratory muscles. The upper body muscles and arms are used for many activities of daily living. Patients with airflow obstruction may develop severe breathlessness and dyssynchronous movements of abdomen and chest wall when using their upper limbs but can perform more exercise when using only their lower limbs[36]. The majority of studies of upper and lower limb training have been undertaken in patients with chronic airflow limitation[37–40]. The overall results demonstrated that improvement was specific to those muscles undergoing training with no associated improvement in respiratory muscle strength or endurance. Conversely, if only upper extremity exercise was undertaken there was no increase in general exercise tolerance although breathlessness and fatigue decreased[38].

The only published weight training study in CF patients resulted in an increase in muscle strength, size and gain in body weight[41]. As in other studies with different exercise training programmes there was a reduction in residual volume which was attributed to increased elasticity and mobility of the chest wall.

The inspiratory muscles sustain the workload of breathing and fatigue when breathing becomes anaerobic. In the early 1960s, it was suggested that breathlessness as a respiratory sensation was related to 'length-tension inappropriateness' of the respiratory muscles[42]. A recent study has shown that breathlessness may be correlated with inspiratory flow in exercising patients with airflow obstruction[43]. The perception that mechanically disadvantaged respiratory muscles may fatigue prematurely as breathing becomes more loaded with severe disease and exercise, has resulted in specific training of these muscles. Early studies of specific inspiratory muscle training in CF patients using normocapnic hyperpnoea or inspiratory resistances, demonstrated an improvement in respiratory muscle strength and endurance[44,45]. There was no improvement in general exercise capacity and evaluation of delay in muscle fatigue was inconclusive. The patients also found breathing through inspiratory resistances tedious. A more recent study evaluated inspiratory muscle training in young children[46]. The study group showed an improvement in inspiratory muscle strength, pulmonary function and exercise tolerance. The increased exercise tolerance has not been observed in previous studies and was related to the length of the study and the increase in total lung capacity. However, Lands *et al.* also found that the strength of inspiratory muscles of CF patients was preserved and fatigue patterns were normal. They questioned the value of training these muscles further[47]. As noted, some CF patients with severe disease who retain CO_2 during exercise alter their breathing into a more comfortable pattern as a compensatory mechanism to the increased work of breathing but do not develop muscle fatigue[14]. Chronic hypercapnia appears to be associated with better survival in COAD: a distinction is necessary between permissive

Table 1 **Some questions for the future directions of cystic fibrosis**

Does exercise reduce mortality?
Does the intensity of exercise matter for respiratory and skeletal muscles?
Does the type of training matter?
Does exercise induced oxygen desaturation matter?
Do the components of ventilation change with training?
Can breathing patterns be changed to relieve dysponea?

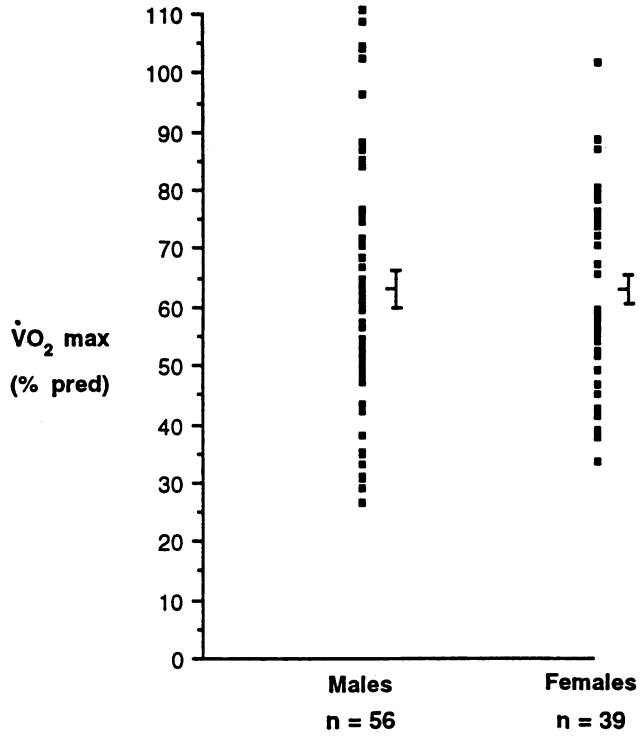

Figure 1 **Cardiorespiratory fitness for males and females attending the Manchester adult CF unit. VO_2 max% predicted mean (SE). Reproduced with the permission of Chapman Hall**

hypercapnia and progressive hypercapnia leading to respiratory failure[48].

FUTURE DIRECTIONS OF EXERCISE IN CYSTIC FIBROSIS

Considerable knowledge has been acquired from (i) the study of the cardiorespiratory responses to exercise in CF patients and (ii) the benefit from short-term exercise studies. This information has provided the basis for the prescription of safe and effective training programmes. However, many questions regarding the value of exercise in pulmonary rehabilitation remain unanswered (Table 1). The most pertinent question is whether regular exercise will improve survival in CF patients? It has been shown that higher levels of aerobic fitness in CF patients is associated with a significantly decreased risk of dying[49,50]. However, no information was available from these studies about the

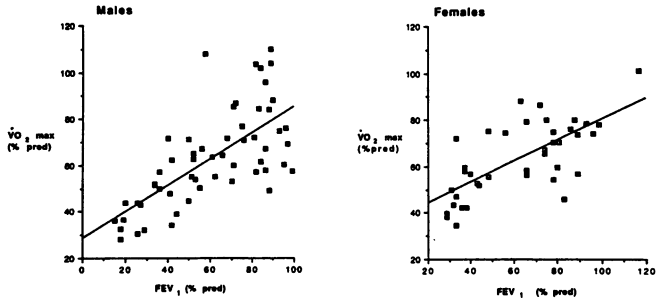

Figure 2 **The relationship between oxygen consumption and spirometry for males and females. There is a wide scatter for oxygen consumption for patients with mild lung disease reflecting a range of fitness levels. For those patients with severe lung disease oxygen consumption is less and approximates tightly with the regression line. Reproduced with the permission of Chapman Hall**

habitual exercise of the fitter patients and whether they were self-selected by virtue of less severe disease. In our unit 98 unselected CF adults (56 M and 39 F) had their fitness assessed with a maximal exercise test (Figure 1). Levels of fitness as reflected by their habitual activity showed a large variation in patients with mild–moderate disease (Figure 2)[51].

There is no evidence that exercise improves lung function in terms of spirometry but if exercise preserved or delayed decline in pulmonary function this would be sufficient to improve survival. Wegener *et al.* showed that exercise capacity corresponded better with clinical ratings of dyspnoea and quality of life than lung function[52]. Severity of lung disease can be used as a predictor of mortality ; patients with an FEV_1 of <30% predicted have a 50% chance of dying within two years[53]. In association with infective exacerbations there may be a decline in FEV_1 of approximately 112 ml/yr[54]. Those exercise studies which have shown either a reduction in residual volume[29,35,41] or an increase in sputum clearance[30,55] with training provide a collective clue as to how exercise may preserve pulmonary function. Exercise improves sputum clearance which maintains collateral ventilation by preventing air trapping and the physiological dead space is minimized. As a consequence, the pathophysiological compensatory changes associated with disease progression, described in the first section, are delayed. The adoption of breathing patterns which are ultimately disadvantageous to the working capacity of the respiratory muscles are forestalled. Currently there are no published prospective long-term studies showing that regular exercise decreases mortality in cystic fibrosis.

If the premise is accepted that exercise is essential therapy, how should exercise be prescribed. In order to acquire fitness, the principles of training dictate exercise should comprise a defined frequency, duration and intensity[56]. Cessation of exercise results in a rapid loss of

all the benefits acquired from training[57]. The progress of fitness training can be monitored by repeat measurements of ventilation and oxygen consumption for a given work rate. Measuring blood lactate levels during exercise of different intensity provides another objective measurement of the progress of training[58]. It is apparent that if exercise has long-term benefits, it should commence during childhood and continue through adulthood. At school participation in sport is usually compulsory but during adulthood this activity declines due to other demands on lifestyle. Encouragement should be given to return to a habitual activity of choice. The patient may ask for advice. From the present evidence, the aim of exercise training should be for endurance rather than strength as this equates better to daily living activities. There should be a general component such as running or cycling and a specific component such as upper body training with weights. How much daily exercise can be achieved will depend upon the motivation and compliance of the individual patient[59].

It is essential that exercise should be recommended for all CF patients. No patient should be excluded from participating in exercise because of disease severity. The severity of lung disease can be defined by a graded exercise test. On the basis of this assessment carefully tailored training programmes can be provided for all patients. Patients with mild to moderate disease can safely be prescribed levels of exercise similar to healthy controls although the maximum work rate and oxygen consumption achieved may be less[26,27]. The objective in patients with mild to moderate disease is to institute and maintain exercise through childhood and adult life and prevent progression of pulmonary disease.

The goals of exercise for patients with severe disease may be different. As their lungs deteriorate they become increasingly breathless, immobilized and quality of life declines. The sensation of breathlessness is modulated by multiple factors but during exercise, thresholds of dyspnoea may be specifically related to the ventilatory patterns of breathing; tidal peak inspiratory flow and breathing frequency. Flow is identified as the most relevant component of the relationship between ventilation to dyspnoea[43]. If breathlessness can be diminished by encouraging exercise then quality of life can be improved.

Several approaches can be adopted to training the breathless patient. It has been shown that by reducing the intensity of exercise but increasing the duration, the muscular effort of breathing and associated dyspnoea are reduced to less than a third[60]. However, if the training is directed specifically at the inspiratory muscles in COAD patients, dyspnoea is reduced and power increased but the pattern of breathing is altered to cope better with an increasing load (exercise or infection) so forestalling muscle fatigue[61].

The oxygen cost of the respiratory muscles is high for CF patients with severe disease. Supplemental oxygen has been shown to lower the cost of ventilation in CF patients by minimizing oxygen desaturation[62] and enabling a longer duration of exercise[63]. The provision of oxygen will increase patient mobility. For those patients awaiting transplantation the ability to increase mobility will make them fitter for the rigours of surgery. Another mechanism for alleviating the respiratory work of breathing during exercise is the application of continuous positive airway pressure (CPAP)[64]. The benefits of CPAP were specific to CF patients with severe disease and resulted in a reduced oxygen consumption, dyspnoea and transdiaphragmatic pressure with an increase in exercise tolerance.

CONCLUSION

The continuing vigorous research into exercise demonstrates how many questions both physiological and medical still need evaluating. Short-term trials over the last decade have clearly established that fitness through training can be achieved for motivated patients with all levels of disease severity. Care must be taken that by adding another discipline to the treatment of CF patients the burden does not become too onerous and create resentment. Although the object of a novel treatment for cystic fibrosis is to increase survival, it is equally important to improve morbidity for a disease where median survival is only into the third decade of life. The quality of well being scale (QWB) has been previously validated[65] and used subsequently to measure the quality of life in CF patients according to mobility, physical activity and social activity[66]. Although the QWB scale correlated significantly with pulmonary function and exercise tolerance it also incorporated other non-pulmonary dimensions just as important to the quality of life of CF patients. It is important to understand that quality of life may not depend upon increasing functional activity. Some patients choose deliberately not to participate in physical activity and are totally content.

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